

Quantifying the impact of dengue containment activities using high-resolution observational data

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Abstract

Dengue virus causes over 96 million cases worldwide per year and is expanding rapidly in geographic range, especially in urban areas. Containment activities are an essential part of reducing the public health burden caused by dengue, but systematic evidence on the comparative efficacy of activities from the field is lacking. To our knowledge, the effect of containment activities on local (sub-city) scale disease dynamics has never been systematically characterized using empirical containment and case data. We combine data from a comprehensive dengue containment monitoring system with confirmed dengue case data from the local government hospitals to estimate the efficacy of seven common containment activities in two urban areas in Pakistan. We use a modified version of the time series Suspected Infected Recovered framework to estimate how the reproductive number, R_0 , of the outbreak changed in relation to deployment of each containment activity. We also estimate the spatial dependence of cases based on deployment of each containment activity. Both analyses suggest that activities aimed at the adult phase of the mosquito lifecycle have the highest efficacy, with fogging having the largest quantifiable effect in reducing cases immediately after deployment. In examining the efficacy of containment activities contemporaneously deployed in the same locations, results here can guide recommendations for future deployment of resources during dengue outbreaks in urban settings.

Keywords: Dengue, containment, spatial statistics, timeseries

1. Introduction

Dengue is a global threat; rapidly spreading with more than one half of the world's population at risk for infection [1, 2]. Dengue virus is the most ubiquitous human arbovirus. It is transmitted primarily by *Aedes aegypti* mosquitoes, a vector which also transmits several other global threats including Zika, chikungunya and yellow fever [3]. Today, severe dengue is a leading cause of hospitalization and death among children and adults in urban areas in Asia, and Central and South America [4]. Dengue disproportionately affects urban areas in developing countries, which often have limited resources for containment and intervention activities [5, 6].

To date, the most common approach to reducing the burden of dengue is through prevention and containment of the vector population [7, 8]. Containment activities focused on vector control broadly fall into three categories: (i) activities targeted at reducing mosquito breeding sites (source reduction); (ii) activities targeted at the larval stage of the vector; and (iii) activities targeted at the adult stage of the vector [9]. While recent work has advanced efforts such as vaccines, genetically modified mosquitoes and Wolbachia-infected mosquitoes [10], these interventions are generally seen as a complement to containment activities [11], and may be prohibitively costly for many countries [12].

Despite the widespread use of containment activities, costing millions of dollars each year, the evidence base of how these activities reduce dengue risk is very limited. Existing research has largely focused on small controlled trials that estimate the effect of a containment activity by comparing treated and untreated populations [13, 14, 15, 16, 17]. Given the systematized nature of such studies, they generally focus on a small number of containment activities in a local, controlled environment; therefore the results may not be directly applicable to real-world settings, where external factors may impact the efficacy of the containment activities [18]. Further, nearly all efforts to quantify the effect of activities on vector control use markers of vector presence (e.g., household/container indices, Breteau indices) as the main outcome of measure, and do not incorporate disease incidence directly [19]. However, the link between vector measurements and dengue risk is poorly understood and a recent systematic review found little evidence of entomological indices such as the Breteau index being statistically associated with risks of dengue transmission [20, 21].

Here, we harness data from a novel containment monitoring system in

38 two cities in Pakistan which has produced data on millions of instances of
39 seven different types of containment activities, each linked with precise geo-
40 location information. In parallel, there is detailed geo-location information on
41 when and where dengue cases occurred in the cities. This provides a unique
42 opportunity to estimate the impact of the different containment activities on
43 the spatial distribution of cases, which we do using two statistical frameworks.

44 This study, as far as we are aware, considers the largest number of
45 dengue containment activity types and instances alongside real field case
46 data. Though the application and results are derived for dengue fever, this
47 approach and findings can be informative for containment activity deploy-
48 ment for other arboviruses. Broadly, the results provide insight which can
49 be used to help shape increasingly important decisions for resource alloca-
50 tion in Pakistan and other countries at risk of dengue and other vector-borne
51 diseases.

52 **2. Results**

53 To quantify the impact of containment activities on disease incidence, we
54 use data on 10,888 confirmed geocoded dengue cases reported in the cities
55 of Rawalpindi (N=7,890 between January 1, 2014 and December 31, 2017,
56 Fig. S3 and Fig. S5) and Lahore (N=2,998 between January 1, 2012 and
57 December 31, 2017, Fig. S2 and Fig. S4). After a major dengue outbreak
58 in 2011, the city of Lahore experienced two mild outbreaks in 2013 and 2016
59 while Rawalpindi has experienced outbreaks in each year since 2014. In
60 addition, the date and precise location of 3,977,159 containment activities
61 was recorded from the two locations (1,610,941 between January 1, 2014
62 and December 31, 2017 from Rawalpindi and 2,366,218 between January 1,
63 2012 and December 31, 2017 from Lahore) (Fig. S4, Fig. S5, [Methods](#),
64 [Supplementary Text](#) and [Table S1](#)).

65 *2.1. Spatial Signature of Containment Activities*

66 To understand the spatial effect of containment activities, we adapt an
67 approach previously used to assess dengue spatial dependence at small spa-
68 tial levels [[22](#), [23](#)]. The spatial dependence metric, τ , quantifies how the
69 location and time of a case relates to the location and time of other cases.
70 Specifically, $\tau_i(d_1, d_2, t_1, t_2)$ is the relative probability of a case being reported
71 in the distance window between d_1 and d_2 , for cases i , within 30 days ($t_2 - t_1$,
72 where t_1 is the day when the case i developed first symptoms) compared to

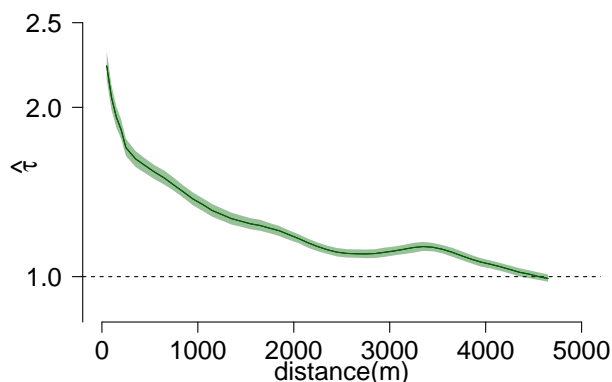


Figure 1: Spatial dependence of cases occurring within 30 days (cases from Lahore and Rawalpindi). The spatial window of the analysis ($d_2 - d_1$) is maintained at 500 m when d_2 is greater than 500 m, and observations are made by sliding the window at intervals of 100 m. For d_2 less than 500 m, d_1 is equal to zero and observations are made by increasing d_2 at intervals of 100 m. Spatial dependence estimates are plotted at midpoint of the spatial window. The time window $t_2 - t_1$ is set to 30 days. 95% CI from bootstrapping 100 replications is shown as green shaded area around estimate.

73 the expected probability of a case if there is no spatial dependence (the case
74 clustering process is independent of space and time). Importantly, both the
75 numerator and denominator of this metric are dependent on the spatiotem-
76 poral distribution of cases appearing in the same area and time-window,
77 therefore controlling for exogenous heterogeneities that could create spatial
78 or temporal clustering (e.g., variation in population density, hospital and
79 healthcare use and reporting rates, and dengue seasonality). All details are
80 explained in [Methods](#) and follow previous work [22].

81 We first calculate the spatial dependence between cases overall, and then
82 specifically for cases in each of Rawalpindi and Lahore ([Methods](#)). Overall,
83 when considering combined patients from both cities, we observe a 2.25 times
84 (95% CI 2.16-2.33) increased probability of observing a case occurring within
85 50 m ($d_1=0$ m and $d_2=100$ m) radius and within 30 days of an index case,
86 relative to the probability of a case occurring if clustering is independent in
87 space and time, highlighting a strong spatial dependence between cases (Fig.
88 1). This falls to 1.37 (95% CI 1.33-1.40) at a distance of 1.25 km ($d_1=1$ km
89 and $d_2=1.5$ km) and 1.0 (95% CI 0.98-1.02) at a distance of 4.55 km ($d_1=4.3$
90 km and $d_2=4.8$ km). When calculating spatial dependence separately for
91 cases in each city, we observed a 2.21 times (95% CI 2.14-2.28) and 1.46

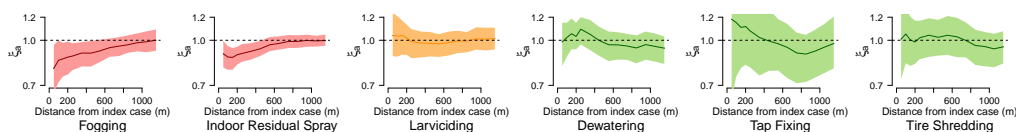


Figure 2: Variation in the effect of containment activity, ξ_{act} , versus the distance (in meters) from index cases using combined data from Rawalpindi and Lahore. Values of ξ_{act} are calculated using control and containment cases which appear in an $m=1000$ m radius of each other. The spatial window of the analysis ($d_2 - d_1$) is maintained at 500 m when d_2 is greater than 500 m, and observations are made by sliding the window at intervals of 100 m. For d_2 less than 500 m, d_1 is equal to zero and observations are made by increasing d_2 at intervals of 100 m. Spatial dependence estimates are plotted at midpoint of the spatial window. Values below 1 show a lower probability of new cases appearing around a case in proximity of a containment activity, compared to a control case. The time window $t_2 - t_1$ is set to 30 days. 95% CI from bootstrapping 100 replications are shown as shaded areas around estimates. Activities targeted at adult stage of mosquito are shaded red, activities targeted at larval stage shaded orange, and activities targeted at source reduction are shaded green.

92 times (95% CI 1.29-1.59) increased probability of observing a case occurring
 93 within 50 m ($d_1=0$ m and $d_2=100$ m) radius and within 30 days of an index
 94 case (Fig. S6) in Rawalpindi and Lahore, respectively. The lower level of
 95 spatial dependence in Lahore, as compared to Rawalpindi, suggests variation
 96 in spatial dependence of cases, across different locations and times, should
 97 be accounted for when studying the effect of containment activities.

98 We then study the result of different containment activities on the spatial
 99 dependence between cases. Of the 9,268 geo-tagged cases in Rawalpindi and
 100 Lahore between 2014 and 2017, 531 were assigned IRS, followed by larviciding
 101 ($n=275$) and fogging ($n=162$) (Table S2). A total of 742 cases had multiple
 102 containment activities in their spatio-temporal proximity and hence were
 103 not used as index cases in the study. As underlying spatial dependence may
 104 differ by different areas in the city or at different times during an epidemic
 105 season, for each case where a containment activity was performed, we identify
 106 a matched control where no activity occurred. Matched-controls occurred
 107 within 30 days and 1000 m of the containment-case but which were not in
 108 immediate vicinity of any containment activities. We define $\xi_a(d_1, d_2)$, as the
 109 ratio of the spatial dependence in distance window d_1 and d_2 , as measured
 110 through τ , for cases which were in proximity of containment activity a , to
 111 the same measure for the matched control. Values of ξ_a below 1 signify that

112 the relative probability of new cases appearing around a case which was in
 113 proximity of a containment activity is lower compared to that of a control
 114 case, after adjusting for underlying clustering in space and time, which is
 115 consistent with a positive impact from the containment activity. Values of
 116 ξ_a around 1 indicate no impact of the activity.

117 We calculate the ξ_a values for each containment activity, a , using com-
 118 bined data from both cities and for each city separately (Fig. 2, Fig. S7 and
 119 Fig. S8). When considering combined data, we find a consistent reduction in
 120 probability of new dengue cases in proximity of indoor residual spray (IRS)
 121 and fogging (Fig. 2). There was a 0.9 reduced probability of a case occurring
 122 within 50 m ($d_1=0$ m and $d_2=100$ m) and in the next 30 days of cases for
 123 which IRS occurred immediately after and in the immediate vicinity (95%
 124 CI: 0.81-0.99) (details in Methods). For fogging, this value was 0.80 (95%
 125 CI: 0.66-0.96). By 750 m ($d_1=500$ m and $d_2=1000$ m) for IRS and 1050 m
 126 ($d_1=800$ m and $d_2=1300$ m) for fogging, there was no difference ($\xi_a=0.99$) in
 127 probability of new cases around the containment cases and the controls (Ta-
 128 ble S3). In contrast to fogging and IRS, there was no consistent reduction in
 129 probability of new cases in proximity of any other containment activity (Fig.
 130 2). This lack of effect is most clearly visible for larviciding which had the
 131 most number of cases amongst activities which had no effect ($n=275$). Due
 132 to the low number of cases in proximity of tap fixing ($n=25$), the resulting
 133 plot for this activity indicate structural uncertainty and are not interpretable.
 134 Findings were consistent when we varied the maximum distance of matched
 135 controls (Fig. S9) and when considering cities separately (Fig. S7, Fig. S8
 136 and Table S2).

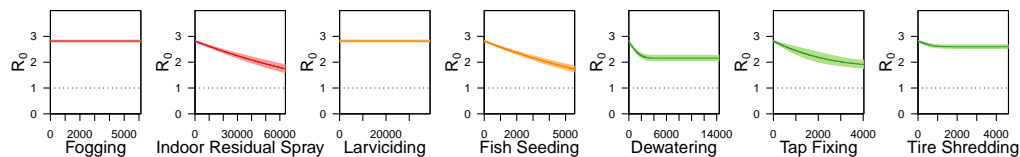


Figure 3: Variation in reproductive number (R_0) of dengue, with variation in instances of containment activity, estimated from the model trained using data from ($N=10$ spatial units) in Lahore between 2012 and 2017, and ($N=14$ spatial units) in Rawalpindi between 2014 and 2017. X-axis represents the total number of containment activities performed, in a spatial unit, in a lagged time step and any residual effect from previous weeks.

137 *2.2. Impact of Containment Activities on R_0*

138 To understand the effect of containment activities on the transmission
139 potential of the outbreak and cases over time, we fit a Time Series Suscep-
140 tible Infected Recovered (TSIR) model for sub-city spatial units from both
141 cities ([Methods](#)) using the adjusted reported cases. Additionally, we create
142 separate TSIR models for each city (Supplementary Text).

143 This modeling approach is useful as it allows us to account for envi-
144 ronmental drivers, which are very pertinent in dengue epidemiology, and it
145 assesses transmission potential through a standardized metric, R_0 . In both
146 Lahore and Rawalpindi, we observe high dengue activity during the post
147 monsoon months, September-November, which highlights the importance of
148 climate in the reproduction of dengue vector (Fig. S2 and Fig. S3). Given
149 that nearly half of dengue cases are asymptomatic and given that our dataset
150 primarily comprises of data from public hospitals, we adjust the reported
151 cases for under-reporting ([Methods](#) and Supplementary Text) [1]. We also
152 assessed sensitivity of results based on this reporting rate; showing no changes
153 in the overall results (Fig. S14).

154 Each city is divided into spatial units ($N=10$ for Lahore and $N=14$ for
155 Rawalpindi), based on administrative boundaries to model localized dengue
156 transmission. We included containment activities, environmental data (tem-
157 perature and rainfall), and population density as part of the model to identify
158 the effect of each of these parameters. Appropriate delays, to account for vec-
159 tor life cycle and transmission of virus from vector to human were added, and
160 the residual effect of containment activities was accounted for, to model re-
161 alistic transmission of dengue accurately infer the effect of each parameter
162 (Supplementary Text). To access the utility of containment data, we train
163 additional variants of the TSIR model using only environmental parameters
164 and population density.

165 The model trained on data from spatial units from both cities, using only
166 environmental parameters and population density, provided a good fit (ad-
167 justed $R^2 = 0.63$), and the addition of containment activities to the model
168 improved the fit (adjusted $R^2 = 0.65$). For the model trained only on data
169 from spatial units in Rawalpindi, the addition of containment activities im-
170 proved the adjusted R^2 from 0.78 to 0.81. Similarly, for Lahore the model
171 incorporating containment activities improved the adjusted R^2 from 0.73 to
172 0.76 (Akaike information criterion (AIC) values also reported in Table S7).

173 Overall, for the model trained on combined data, the reproductive num-
174 ber was 2.82 (at mean temperature and precipitation values; 25.5 Celsius

175 and rainfall for 2 days during a 2 week period), if all containment activity
176 coefficients are set to zero. For Lahore the R_0 was 1.59 (at 26 Celsius and 2
177 days of rainfall), and for Rawalpindi the R_0 was 1.79 (at 24.9 Celsius and 2
178 days of rainfall).

179 Our results illustrate varied relationships between an increase in the
180 amount of containment activities and cases over time, for each activity as it
181 was deployed in Lahore and Rawalpindi, and using R_0 (Fig. 3, Fig. S12 and
182 Fig. S13). We quantify the amount of a containment activity in instances,
183 where an instance during a single time-step (2 weeks in our study) represents
184 the sum of the number of activities performed during the time-step, and the
185 residual effect of any activities performed in previous weeks (Supplementary
186 Text). For example for fogging, which has no residual effect, an instance at
187 time t represents only the number of activities performed in a spatial unit
188 at t . In contrast, for IRS which has a residual effect, instances at time t
189 represent the sum of the number of IRS activities performed at time t and
190 the residual effect of IRS activities performed in the previous six time-steps
191 (the residual effect of IRS is three months).

192 Of the adulticides, we find an increase in IRS to be related to a decrease
193 in R_0 of dengue in both Lahore and Rawalpindi, as well as when data from
194 both cities is modelled as part of a single model. Specifically, additional
195 deployment of approximately 4,800 IRS activities in a spatial unit was related
196 to a 0.1 decrease in the R_0 of dengue. In contrast, fogging was related
197 to a decrease in the R_0 of dengue only in Lahore. Among containment
198 activities targeted at the larval stage of mosquitoes, larviciding showed no
199 effect on R_0 in either city or when data from both cities was trained together,
200 while fish seeding was only related to a decrease in R_0 when data from both
201 cities was trained in a single model. Among source reduction activities, tap
202 fixing was related to a decrease in R_0 in Lahore and in the model with
203 combined data from both cities. Tire shredding was related to a decrease
204 in R_0 in Rawalpindi, and when analyzing combined data from both cities,
205 but the effect of this activity was not statistically significant in Rawalpindi.
206 Dewatering was only related to a decrease in R_0 when data from both cities
207 was trained in a single model. Results across all models are summarized in
208 Table S4.

209 3. Discussion

210 Data from the dengue containment activity monitoring system deployed
211 in the Punjab province, Pakistan in 2012 was used; which, to our knowledge,
212 monitors the largest number and types of containment activities. The system
213 captured millions of containment activity events over a seven-year period
214 (Table S1), each event linked to precise geo-coordinates. Combined with
215 geo-location of patients, this allowed us to systematically examine the effect
216 of multiple containment activities on sub-city scale disease dynamics, which
217 has never before been characterized using empirical activity and case data.

218 We examined the relationship between deployed instances of each contain-
219 ment activity type and the spatial dependence of geo-located dengue cases
220 in their proximity, in the cities of Rawalpindi and Lahore between 2014 and
221 2017. This method allows generation of unbiased estimates in the midst of
222 exogeneous heterogeneities that could create spatial or temporal clustering
223 (e.g., variation in population density, hospital and healthcare use and report-
224 ing rates, and dengue seasonality). The result is quantification of both the
225 maximum reduction in dengue transmission in the vicinity of a particular
226 type of activity, as well as the maximum distance at which this reduction in
227 dengue transmission is evident. Notably, the method and results provides
228 novel empirical results insights into the comparative efficacy of fogging and
229 indoor residual spray using real case and containment activity data.

230 The time series modelling of dengue cases in Lahore and Rawalpindi en-
231 abled us to assess the relation between the R_0 of dengue and amount of
232 containment activities, as deployed. Results from this approach are based
233 on empirical field data, consider multiple interventions and use a precise and
234 standardized measure of efficacy (R_0) in contrast to studies based on sim-
235 ulated data and models, or using proxy measures for dengue transmission
236 [19]. The results show that training a separate model for spatial units in
237 each city provides a better fit to data and hence results from models trained
238 for individual cities get precedence over the model trained on combined data.

239 The spatial dependence of dengue cases reported here is consistent with
240 that reported in previous work using dengue case data from Bangkok. The
241 spatial dependence at 200 m, presented in [22] is 1.82 (95% CI: 1.45-2.16) is
242 comparable to 1.87 (95% CI: 1.81-1.93) observed in the two cities in Pakistan
243 in our study. Further, the values of 1.83 and 1.45 observed in Rawalpindi and
244 Lahore respectively also lies within the confidence interval. Results from the
245 spatial signature analysis show that application of IRS and fogging spray,

246 in the vicinity of a dengue case, result in reduction of the generation of
247 new cases by 10% and 20% respectively. Additionally, IRS and fogging are
248 shown to be effective (ξ_a below 1) up to a distance of 750 m and 1050 m
249 respectively. Similar trends are observed based on the results of time series
250 modelling of containment activities. Increases in IRS and fogging are re-
251 lated to decreases in the reproductive number of dengue in Lahore, though
252 results from Rawalpindi specific model only show a statistically significant
253 effect from IRS. This could be due to the fact that TSIR models assume
254 that activities and cases are uniformly distributed in each spatial unit con-
255 sidered. If the assumption is violated and activities are not performed in the
256 direct vicinity of cases, then the resulting effect from the model may not be
257 completely accurate [24].

258 Results from both the spatial dependence method and timeseries mod-
259 elling did not find larviciding to be effective. These results are consistent
260 with a recent systematic review, which found Temephos (a chemical used
261 in larviciding) to be only effective in reducing entomological indicators, but
262 found no evidence of its association with reduction in disease transmission.
263 At the same time, the results highlight that while containment activities can
264 be effective under laboratory conditions, the effectiveness does not translate
265 exactly in the field in reducing dengue transmission. This signifies the utility
266 of studies such as this which examine effectiveness of containment activities
267 using real case data. For example, there is conflicting evidence regarding
268 the effectiveness of fish seeding in the literature [13, 25]. Our time series
269 method did not find fish seeding to be effective in either city, and due to a
270 minimal number of cases which were adjacent to only fish seeding activities,
271 no inference about the effectiveness of fish seeding could be made from the
272 spatial dependence method.

273 Among source reduction containment activities, we find no activity to
274 be effective using the spatial dependence method. Using the TSIR model,
275 we find an increase in tap fixing in Lahore and increase in dewatering in
276 Rawalpindi to be associated with a decrease in the reproductive number of
277 dengue.

278 Quantitatively, our results corroborate existing knowledge about the role
279 of rainfall and temperature in dengue transmission by showing increases in
280 R_0 with increases in temperature and number of rainfall days [26, 27] (Sup-
281 plementary Text). We also find an increase in population density is related
282 to an increase in R_0 , when considering data from both cities separately (Sup-
283 plementary Text).

284 It should be noted that results from this study are only relevant to the
285 spatial dependence of cases or relationship between containment activity de-
286 ployment and R_0 after dengue cases have started to appear. Results from
287 the study do not explain the effect of a containment activity on the overall
288 dengue burden, or on delaying or preventing the appearance of first cases.
289 A separate, and longitudinal analysis would be required to evaluate the pre-
290 ventive effectiveness of each containment activity. As well, as with any study
291 based on human reported data, there could be a chance of sampling bias in
292 the containment activity reports. Such a bias would have to have a system-
293 atic spatial or temporal dependence in order to impact results; thus we deem
294 the assumption that such a bias would not affect the results fair. Further,
295 while we consistently observe a short-term positive impact of IRS on dengue
296 incidence, we were unable to assess the longer-term impact of the contain-
297 ment activities and we cannot rule out these containment activities simply
298 delay infection to future time points [28].

299 In conclusion, results of this study regarding the relationship of different
300 containment measures with the spatial dependence of dengue cases or the R_0 ,
301 provide specific insight regarding dengue in urban settings. More broadly,
302 these results and the models and methods used to derive them – are relevant
303 to a growing number of global health concerns related to the *Aedes aegypti*
304 mosquito, including the Zika virus and chikungunya, which are also known to
305 particularly impact urban areas. Further, the methods presented in the work
306 lay groundwork for future studies aimed at studying the effect of containment
307 from observational data collected from the field.

308 4. Methods

309 4.1. Containment Activities Data

310 Modern technology was applied by the Punjab Information Technology
311 Board to track containment activities carried out by the Punjab Health De-
312 partment. Mobile phones were distributed to health care workers to record
313 their activities since 2012 using a mobile application (Supplementary Text
314 and Fig. S1). Government workers were asked to take a picture before and
315 after performing the containment activity as a verifiable proof that the ac-
316 tivity had been performed (Supplementary Text). Global positioning system
317 (GPS) coordinates of the location, time stamp, and pictures of the performed
318 activity were automatically submitted to a centralized server where they were
319 monitored. Data on dengue containment activities for the period January 1,

320 2012 to December 31, 2017 was received. This consisted of 7,281,932 con-
321 tainment records, each including the name of the containment activity, a
322 time stamp of when the activity was performed and the GPS coordinates
323 for the location of where it was performed. After excluding those activities
324 performed outside the boundaries of the two cities, we were left with a total
325 of 2,366,218 containment activity instances in Lahore between January 1,
326 2012 and December 31, 2017, and 1,610,941 activity instances performed in
327 Rawalpindi between January 1, 2014 and December 31, 2017. For the TSIR
328 model, we used the GPS coordinates to map each containment activity data
329 point to a spatial unit.

330 4.2. *Epidemiological data*

331 Data regarding confirmed dengue cases, for the same time period as the
332 containment activities, was retrieved from the Government of Punjab's cen-
333 tralized patient portal system. Precisely geo-tagged information linked to
334 each case was available starting in 2014 (spatial unit level data was available
335 from 2012-2014 for Lahore) (Supplementary Text). A total of 2,998 cases
336 were reported in Lahore between January 1, 2012 and December 31, 2017.
337 In Rawalpindi a total of 7,890 confirmed dengue cases were reported and
338 geo-tagged between January 1, 2014 and December 31, 2017.

339 4.3. *Environmental Data*

340 City-wide daily mean temperature and mean precipitation estimates, for
341 both cities, were obtained from the Pakistan Meteorological Department for
342 time series method (www.pmd.gov.pk accessed August 27, 2018). As pre-
343 viously shown these climate factors directly affect mosquito survival, repro-
344 duction, and development and thus their abundance.

345 4.4. *Spatial Dependence of Cases*

346 First, to characterize the spatial dependence of cases we compute the
347 probability of a case occurring between times t_1 and t_2 , and within distance
348 range d_1 and d_2 of a given case versus the expected probability if the clus-
349 tering processes were independent in space and time:

$$\tau_i(d_1, d_2, t_1, t_2) = \frac{Pr(\Omega_i(d_1, d_2, t_1, t_2))}{Pr(\Omega_i(d_1, d_2, \cdot, \cdot))Pr(\Omega_i(\cdot, \cdot, t_1, t_2))} \quad (1)$$

350 where $\Omega_i(d_1, d_2, t_1, t_2)$ is the set of cases between d_1 and d_2 (in meters) and
351 temporal window of t_1 and t_2 (in days) of case i ; $\Omega_i(\cdot, \cdot, t_1, t_2)$ is the set of cases

352 in temporal window t_1 to t_2 of case i independent of space, and $\Omega_i(d_1, d_2, \cdot, \cdot)$
353 the set of cases within spatial window d_1 and d_2 of case i , independent of
354 time. For our analysis, we use a fixed time window of 30 days: t_1 is selected
355 as the day when the patient experienced first symptoms of dengue virus, and
356 $t_2 = t_1 + 30$. This time window is chosen to ensure that cases considered are
357 from the same transmission chain, though we perform sensitivity analysis
358 using additional time windows (Fig. S10). Dependence is then observed
359 across variation in the distance window.

360 Then, the overall spatial dependence of new cases appearing around cases
361 labelled s (labelling is defined in the next subsection) is estimated as:

$$\hat{\tau}_s(d_1, d_2, t_1, t_2) = \frac{(\sum_{i=1}^N |\Omega_i(d_1, d_2, t_1, t_2)|z_i) \cdot (\sum_{i=1}^N |\Omega_i(\cdot, \cdot, \cdot, \cdot)|z_i)}{(\sum_{i=1}^N |\Omega_i(d_1, d_2, \cdot, \cdot)|z_i) \cdot (\sum_{i=1}^N |\Omega_i(\cdot, \cdot, t_1, t_2)|z_i)} \quad (2)$$

362 where z_i is 1 if the case is labelled s , N is the total number of cases in the
363 dataset regardless of their label, and $\Omega_i(\cdot, \cdot, \cdot, \cdot)$ is the set of all cases in the
364 dataset.

365 4.5. Spatial Signature of Containment Activities

366 To identify the impact of containment activities on the spatial dependence
367 of dengue cases (the “spatial signature” of an activity) we first label all
368 cases in the dataset as either a “containment” or a “control”. A case is
369 labelled as $s = a$ if only the containment a was performed in a 20 meter
370 radius and time window of the past 30 days of the case before the first
371 symptom appeared. Only cases for which a single containment activity was
372 performed in the surrounding area are included in the analysis, to ensure
373 only the effect of a single type of containment activity is being measured. A
374 case is labelled a control, $s = c$, if no containment activity was performed in
375 a 20 meter radius and time window of the past 30 days of the case before
376 the first symptom appeared. The *tau* metric measures clustering dynamics,
377 however there are factors such as population variation, reporting biases and
378 availability of vegetation and water for growth of vector, can also play a role
379 in variation of the number of cases that would be expected in a given location
380 and time. Thus, to compare clustering while controlling for such factors, we
381 compare clustering around cases that have a similar epidemiological context.
382 For a given set of containment cases labelled a , we select a subset of cases,
383 a' , such that each case in a' has a matching control case. A matching control

384 case is defined as a control case which is within a radius of m meters, and
385 was reported within 30 days of the containment case. We assess how values
386 of m of 500, 1,000 and 2,000 (Fig. 2 and Fig. S9) impact the results. For
387 each containment case a' , we randomly select a matching control case and
388 represent the set of matching control cases as c'_a . The spatial signature of
389 containment activity a , ξ_a , is then calculated as:

$$\xi_a = \frac{\hat{\tau}_{a'}}{\hat{\tau}_{c'_a}} \quad (3)$$

390 4.6. Impact of Containment Activities on R_0

391 We model the incidence of dengue using a time-series susceptibleinfect-
392 edrecovered (TSIR) model of viral incidence previously used to reconstruct
393 dengue dynamics in Asia (Supplementary Text) [29, 30]. The city of La-
394 hore is divided in ($n=10$) and the city of Rawalpindi in ($n=14$) spatial units,
395 and localized transmission of dengue is modelled at each spatial unit. The
396 reported cases, in each spatial unit, are first reconstructed to account for
397 under-reporting. The reported number of cases, $I_i^{(r)}(t)$, are first smoothed,
398 then multiplied with the inverse of the reporting rate rr , and the product
399 is used as the mean of Poisson distribution (Supplementary Text, and Table
400 S5 and S6). The number of infected individuals, $I_i(t)$, are selected at each
401 time step from the distribution. This reconstruction methodology, used in
402 previous infectious disease modeling work [31], gives the advantage of captur-
403 ing tails of the epidemic curve in a realistic, continuous manner. Our model
404 incorporates environmental parameters in the transmission rate to account
405 for variation in vector population density. We use two weeks as the time step
406 in our study, consistent with the generation interval and previous studies
407 which model the transmission of dengue [32, 30] (Supplementary Text). The
408 general TSIR model is defined via the following equations:

$$I_i(t+1) = \beta_i(t) \frac{S_i(t)}{N_i(t)} I_i^{\alpha_i}(t) \epsilon \quad (4)$$

409

$$S_i(t) = S_i(t-1) - I_i(t) + \rho N_i(t-1) - \phi S_i(t-1) \quad (5)$$

410 where $I_i(t)$, $S_i(t)$ and $N_i(t)$ are the infected, susceptible and total population
411 during time step t in spatial unit i , ρ is the bi-weekly birth rate, ϕ is the bi-
412 weekly death rate, α_i is the mixing coefficient in spatial unit i , and $\beta_i(t)$ is the

413 transmission coefficient during time step t . The error term ϵ is assumed to
414 be an independent and identically log-normally distributed random variable.

415 We endogenize containment activities in the transmission coefficient $\beta_i(t)$.
416 This decision reflects the fact that containment activities reduce the contact
417 rate between humans and mosquitoes, which results in a reduction of the
418 transmission rates from human to mosquito to human [33]. The transmission
419 coefficient β for equation 4 is parameterized as:

$$\log(\beta_i(t)) = \sum_a \theta_a C_{i,a}(t - l_a) + \sum_j \theta_j E_j(t - l_j) + \theta_p D_i(t) \quad (6)$$

420 where l_a and l_j are time steps containment activities a and environmental
421 parameters j were lagged respectively (Supplementary Text). $C_{i,a}(t - l_a)$
422 is the number of times per squared kilometer containment activity a was
423 performed in spatial unit i during week $(t - l_a)$. $E_j(t - l_j)$ is the value of
424 environmental parameter j during week $(t - l_j)$. $D_i(t)$ is the population
425 density in spatial unit i . The residual effect of each containment activity is
426 added based on existing knowledge (see section Transmission cycle of dengue
427 and timing and residual effect of containment activities in Supplementary
428 Text).

429 To calculate the value of $\beta_i(t)$, the value of β for each town at each time
430 step, a single model is used to find the best fit for parameters: θ_a , θ_j , θ_p ,
431 based on the number of each containment activity and environmental pa-
432 rameters as well as all non-zero cases data point in each town, i , at every
433 time step (equation 6). We use Shape constrained additive model (SCAM)
434 to fit this relationship. Shape constrained additive models are an extension
435 of generalized additive models (GAMs) which provide the advantage of using
436 existing knowledge about the relationship of the response variable with the
437 explanatory variables [34, 35]. This prevents noise from being included in the
438 shape of splines from the GAM. Containment activities are modeled as mono-
439 tonically decreasing splines while environmental parameters and population
440 density are modeled as monotonically increasing splines. The smoothing pa-
441 rameters are estimated using maximum likelihood. Finally, using estimates
442 of θ_a , θ_j , and θ_p from the SCAM model and equation 6 and 7, we identify the
443 variation in R_0 (reproductive number of dengue) by variation in the amount
444 of each containment activity. The R_0 is calculated by the following equation:

$$R_{0_i}(t) = \frac{\beta_i(t)}{\gamma} \quad (7)$$

445

446 where, γ is the recovery rate and is equal to 1 time step in our study, given
447 the fact that infected patients are immediately admitted in the hospital and
448 removed from the infected population. The reproductive number can be
449 defined as the number of secondary infections a primary infection can cause
450 over the course of its infectious period [36]. If R_0 is greater than 1, then the
451 disease will spread exponentially, while an R_0 below 1 means that the disease
452 will not spread.

- 453 [1] S. Bhatt, P. W. Gething, O. J. Brady, J. P. Messina, A. W. Farlow,
454 C. L. Moyes, J. M. Drake, J. S. Brownstein, A. G. Hoen, O. Sankoh,
455 M. F. Myers, D. B. George, T. Jaenisch, G. R. Wint, C. P. Simmons,
456 T. W. Scott, J. J. Farrar, S. I. Hay, The global distribution and burden
457 of dengue, *Nature* 496 (2013) 504–7.
- 458 [2] M. G. Guzman, E. Harris, Dengue, *The Lancet* 385 (2015) 453–465.
- 459 [3] C. P. Simmons, J. J. Farrar, N. van Vinh Chau, B. Wills, Dengue, *New*
460 *England Journal of Medicine* 366 (2012) 1423–1432.
- 461 [4] C. H. Calisher, Persistent emergence of dengue, *Emerging infectious*
462 *diseases* 11 (2005) 738.
- 463 [5] S. B. Halstead, Selective primary health care: strategies for control of
464 disease in the developing world. xi. dengue, *Rev Infect Dis* 6 (1984)
465 251–64.
- 466 [6] O. Horstick, S. Runge-Ranzinger, M. B. Nathan, A. Kroeger, Dengue
467 vector-control services: how do they work? a systematic literature re-
468 view and country case studies, *Trans R Soc Trop Med Hyg* 104 (2010)
469 379–86.
- 470 [7] D. J. Gubler, Epidemic dengue/dengue hemorrhagic fever as a public
471 health, social and economic problem in the 21st century, *Trends in*
472 *microbiology* 10 (2002) 100–103.
- 473 [8] J. Hemingway, B. J. Beaty, M. Rowland, T. W. Scott, B. L. Sharp, The
474 innovative vector control consortium: improved control of mosquito-
475 borne diseases, *Trends Parasitol* 22 (2006) 308–12.

- 476 [9] W. H. Organization, Regional office for south east asia: Comprehensive
477 guidelines for prevention and control of dengue and dengue hemorrhagic
478 fever: Revised and expanded edition, New Delhi, India 14 (2011) 16.
- 479 [10] A. A. Hoffmann, B. L. Montgomery, J. Popovici, I. Iturbe-Ormaetxe,
480 P. H. Johnson, F. Muzzi, M. Greenfield, M. Durkan, Y. S. Leong,
481 Y. Dong, H. Cook, J. Axford, A. G. Callahan, N. Kenny, C. Omodei,
482 E. A. McGraw, P. A. Ryan, S. A. Ritchie, M. Turelli, S. L. O’Neill,
483 Successful establishment of wolbachia in aedes populations to suppress
484 dengue transmission, *Nature* 476 (2011) 454–7.
- 485 [11] J. Reiner, R. C., N. Achee, R. Barrera, T. R. Burkot, D. D. Chadee, G. J.
486 Devine, T. Endy, D. Gubler, J. Hombach, I. Kleinschmidt, A. Lenhart,
487 S. W. Lindsay, I. Longini, M. Mondy, A. C. Morrison, T. A. Perkins,
488 G. Vazquez-Prokopec, P. Reiter, S. A. Ritchie, D. L. Smith, D. Strick-
489 man, T. W. Scott, Quantifying the epidemiological impact of vector
490 control on dengue, *PLoS Negl Trop Dis* 10 (2016) e0004588.
- 491 [12] J. G. Schraiber, A. N. Kaczmarczyk, R. Kwok, M. Park, R. Silverstein,
492 F. U. Rutaganira, T. Aggarwal, M. A. Schwemmer, C. L. Hom, R. K.
493 Grosberg, et al., Constraints on the use of lifespan-shortening wolbachia
494 to control dengue fever, *Journal of theoretical biology* 297 (2012) 26–32.
- 495 [13] V. M. Azevedo-Santos, J. R. Vitule, E. Garcia-Berthou, F. M. Pelicice,
496 D. Simberloff, Misguided strategy for mosquito control, *Science* 351
497 (2016) 675.
- 498 [14] Y. H. Bang, C. P. Pant, A field trial of abate larvicide for the control of
499 aedes aegypti in bangkok, thailand, *Bull World Health Organ* 46 (1972)
500 416–25.
- 501 [15] W. W. Han, A. Lazaro, P. J. McCall, L. George, S. Runge-Ranzinger,
502 J. Toledo, R. Velayudhan, O. Horstick, Efficacy and community effec-
503 tiveness of larvivorous fish for dengue vector control, *Trop Med Int*
504 *Health* 20 (2015) 1239–1256.
- 505 [16] A. Kroeger, A. Lenhart, M. Ochoa, E. Villegas, M. Levy, N. Alexander,
506 P. J. McCall, Effective control of dengue vectors with curtains and
507 water container covers treated with insecticide in mexico and venezuela:
508 cluster randomised trials, *BMJ* 332 (2006) 1247–52.

- 509 [17] V. C. Pinheiro, W. P. Tadei, Evaluation of the residual effect of temephos
510 on *aedes aegypti* (diptera, culicidae) larvae in artificial containers in
511 manaus, amazonas state, brazil, *Cad Saude Publica* 18 (2002) 1529–36.
- 512 [18] R. Reiner, S. Stoddard, G. Vazquez-Prokopec, H. Astete, T. A. Perkins,
513 M. Sihuincha, J. Stancil, D. Smith, T. Kochel, E. Halsey, et al., Es-
514 timating the impact of city-wide *aedes aegypti* population control: An
515 observational study in iquitos, peru, *bioRxiv* (2018) 265751.
- 516 [19] T. Erlanger, J. Keiser, J. Utzinger, Effect of dengue vector control
517 interventions on entomological parameters in developing countries: a
518 systematic review and metaanalysis, *Medical and veterinary entomology*
519 22 (2008) 203–221.
- 520 [20] L. George, A. Lenhart, J. Toledo, A. Lazaro, W. W. Han, R. Velayudhan,
521 S. Runge Ranzinger, O. Horstick, Community-effectiveness of temephos
522 for dengue vector control: A systematic literature review, *PLoS Negl*
523 *Trop Dis* 9 (2015) e0004006.
- 524 [21] L. R. Bowman, S. Runge-Ranzinger, P. McCall, Assessing the rela-
525 tionship between vector indices and dengue transmission: a systematic
526 review of the evidence, *PLoS neglected tropical diseases* 8 (2014) e2848.
- 527 [22] H. Salje, J. Lessler, T. P. Endy, F. C. Curriero, R. V. Gibbons,
528 A. Nisalak, S. Nimmannitya, S. Kalayanarooj, R. G. Jarman, S. J.
529 Thomas, et al., Revealing the microscale spatial signature of dengue
530 transmission and immunity in an urban population, *Proceedings of the*
531 *National Academy of Sciences* 109 (2012) 9535–9538.
- 532 [23] J. Lessler, H. Salje, M. K. Grabowski, D. A. Cummings, Measuring
533 spatial dependence for infectious disease epidemiology, *PloS one* 11
534 (2016) e0155249.
- 535 [24] C. J. E. Metcalf, V. Andreasen, O. N. Bjørnstad, K. Eames, W. J. Ed-
536 munds, S. Funk, T. Hollingsworth, J. Lessler, C. Viboud, B. T. Grenfell,
537 Seven challenges in modeling vaccine preventable diseases, *Epidemics*
538 10 (2015) 11–15.
- 539 [25] S. N. Surendran, A. Kajatheepan, P. J. Jude, R. Ramasamy, Use of
540 tilapia, *oreochromis mossambicus*, for the control of mosquito breed-

- 541 ing in water storage tanks in the jaffna district of sri lanka, *Tropical*
542 *Medicine and Health* 36 (2008) 107–110.
- 543 [26] R. Bueno-Mari, R. Jimenez-Peydro, Global change and human vulner-
544 ability to vector-borne diseases, *Front Physiol* 4 (2013) 158.
- 545 [27] L. Xu, L. C. Stige, K.-S. Chan, J. Zhou, J. Yang, S. Sang, M. Wang,
546 Z. Yang, Z. Yan, T. Jiang, et al., Climate variation drives dengue dy-
547 namics, *Proceedings of the National Academy of Sciences* 114 (2017)
548 113–118.
- 549 [28] N. Ferguson, Challenges and opportunities in controlling mosquito-
550 borne infections., *Nature* 559 (2018) 490–497.
- 551 [29] B. F. Finkenstdt, B. T. Grenfell, Time series modelling of childhood
552 diseases: a dynamical systems approach, *Journal of the Royal Statistical*
553 *Society: Series C (Applied Statistics)* 49 (2000) 187–205.
- 554 [30] M. U. Kraemer, T. A. Perkins, D. A. Cummings, R. Zakar, S. I. Hay,
555 D. L. Smith, J. Reiner, R. C., Big city, small world: density, contact
556 rates, and transmission of dengue across pakistan, *J R Soc Interface* 12
557 (2015) 20150468.
- 558 [31] T. P. Van Boeckel, S. Takahashi, Q. Liao, W. Xing, S. Lai, V. Hsiao,
559 F. Liu, Y. Zheng, Z. Chang, C. Yuan, et al., Hand, foot, and mouth dis-
560 ease in china: critical community size and spatial vaccination strategies,
561 *Scientific reports* 6 (2016) 25248.
- 562 [32] N. G. Reich, S. Shrestha, A. A. King, P. Rohani, J. Lessler, S. Kalayana-
563 rooj, I.-K. Yoon, R. V. Gibbons, D. S. Burke, D. A. Cummings, Inter-
564 actions between serotypes of dengue highlight epidemiological impact
565 of cross-immunity, *Journal of The Royal Society Interface* 10 (2013)
566 20130414.
- 567 [33] M. L. Ndeffo-Mbah, D. P. Durham, L. A. Skrip, E. O. Nsoesie, J. S.
568 Brownstein, D. Fish, A. P. Galvani, Evaluating the effectiveness of
569 localized control strategies to curtail chikungunya, *Sci Rep* 6 (2016)
570 23997.
- 571 [34] N. Pya, S. N. Wood, Shape constrained additive models, *Statistics and*
572 *Computing* 25 (2015) 543–559.

- 573 [35] S. N. Wood, Modelling and smoothing parameter estimation with mul-
574 tiple quadratic penalties, *Journal of the Royal Statistical Society: Series*
575 *B (Statistical Methodology)* 62 (2000) 413–428.
- 576 [36] C. Fraser, C. A. Donnelly, S. Cauchemez, W. P. Hanage, M. D.
577 Van Kerkhove, T. D. Hollingsworth, J. Griffin, R. F. Baggaley, H. E.
578 Jenkins, E. J. Lyons, T. Jombart, W. R. Hinsley, N. C. Grassly, F. Bal-
579 loux, A. C. Ghani, N. M. Ferguson, A. Rambaut, O. G. Pybus, H. Lopez-
580 Gatell, C. M. Alpuche-Aranda, I. B. Chapela, E. P. Zavala, D. M. Gue-
581 vara, F. Checchi, E. Garcia, S. Hugonnet, C. Roth, W. H. O. R. P. A.
582 Collaboration, Pandemic potential of a strain of influenza a (h1n1):
583 early findings, *Science* 324 (2009) 1557–61.